B3 cont'd

step (ii),
so as to thereby produce recombinant human AChE.--

B4

--26. (New) The transgenic non-human animal of claim 12, wherein the mammal is a mouse.--

REMARKS

Claims 11-14, 17-20 and 23-25 were pending in the subject application. Applicants have canceled claim 25 without prejudice to applicants' right to pursue the subject matter of this claim in a later-filed application. Applicants have also amended claims 11-14, 17-20 and 23-24 and added new claim 26. Support for these amendments may be found inter alia in the specification as follows: for the term "nucleic acid" recited in claims 11, 13 and 14: page 20, line 28; for the term "germ cell" recited in claim 11: page 75, line 16; for the term "somatic cell" recited in claim 11: see generally, page 75, line 32 - page 81, line 33; and for the term "fragment" recited in claim 13: page 55, line 30; page 56, lines 5 and 18. The remaining changes to the claims merely introduce minor grammatical and format changes. In making these amendments, applicants neither concede the correctness of the Examiner's rejections in the June 28, 2001 Final Office Action, nor abandon their right to pursue in a continuing application embodiments of the instant invention no longer claimed in this application. These amendments do not involve any issue of new matter. Therefore, entry of these amendments is respectfully requested such that claims 11-14, 17-20, 23-24 and 26 will be pending.

Response to June 28, 2001 Final Office Action

Formalities

Applicants acknowledge the Examiner's statements that the obviousness type double patenting rejection, the rejection under 35 U.S.C. §101, and the rejection under 35 U.S.C. §112, first paragraph (written description) have been overcome.

In addition, applicants acknowledge the Examiner's statement that applicants' arguments regarding promoter's as set forth in the May 4, 2001 Amendment is persuasive and has been implemented in the scope of enablement below.

Furthermore, applicants acknowledge the Examiner's statement that the claims are free of the prior art. The Examiner stated that at the time of the instant invention the art did not teach or suggest the production of transgenic mice or Xenopus whose genome contained and expressed a DNA sequence encoding any human AChE or human BChE.

Sequence Listing

The Examiner stated that the requirements set forth in 37 C.F.R. §§ 1.821(a)(1) and (a)(2) for sequence rule compliance have been met. However, the Examiner stated that applicants failed to request entry into the specification. The Examiner stated that in response to this office action, applicants should request entry of the Sequence Listing into the specification.

In response, applicants respectfully traverse. Nevertheless, without conceding the correctness of the Examiner's statement but in order to expedite prosecution of the subject application,

applicants have hereinabove requested entry of the "Sequence Listing" into the specification. Accordingly, applicants contend that these remarks obviate the above objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner maintained the rejection of claims 11-14, 17-20 and 23-25 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for transgenic mice and frog tadpoles whose genomes comprise a transgene comprising a promoter operatively linked to a DNA sequence encoding a splice variant of human AchE expressing AchE with acetylcholine esterase activity, wherein said sequence is expressed in cells of said mouse and where said mouse or tadpole exhibits changes in its neuromuscular junction structure, and assay systems of said mouse or tadpole, the specification allegedly does not provide enablement for the preparation and use of transgenic animals comprising any and all variants of said cholinesterase genes or assay systems of these animals for reasons of record. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Examiner stated that the following arguments by applicants are not persuasive: i) that AChE is a secretory extracellular protein, and that the membrane structure is not needed for activity; ii) that glycosylation is not needed for the esterase activity of AChE and that active protein has been produced in E.coli; iii) that AChE has more than one use and that Dr. Soreq has filed other applications relating to neurite growth promotion and neuronal

differentiation activity in progenitor cells.

The Examiner stated that these arguments are not substantiated by declaration or publications, and without substantiation they are not persuasive. Further, the Examiner stated that regardless of the use of the produced AChE, it would need to be active in esterase activity, neurite growth promotion or neuronal differentiation activity. The Examiner stated that while the protein may have several activities, those activities need to be present in the produced protein. The Examiner stated that the predictability of the protein having this activity is the focus one part of the enablement rejection.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claim 25 without prejudice or disclaimer to their right to pursue this claim in a later-filed application.

In addition, applicants respectfully traverse the Examiner's rejection, and maintain that the specification fully enables the preparation and use of transgenic animals comprising any and all variants of said cholinesterase genes; assay systems of these animals; and production of said cholinesterase genes in the milk produced by the transgenic animals. In support of their position, applicants submit a Declaration Under 37 C.F.R. §1.132 (**Exhibit 2**) in which Dr. Hermona Soreq declares that in view of the methods and examples publicly available as of the priority date of the subject application, i.e. February 28, 1994, and the teachings set forth in the subject application, one of skill in the art would have been able to, without undue experimentation: (i) prepare and use any

transgenic non-human animal comprising cholinesterase genes and any variants thereof; (ii) use such transgenic animals as assay systems; and (iii) use such transgenic animals for the production of hAChE in the milk produced by the transgenic animals.

Applicants contend that the above remarks obviate this rejection. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 11, 29, 23 and 25 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner stated that i) claim 11(d) lacks antecedent basis for "said synthetic variants"; ii) claim 19 contains two mentions of "variants of AchE"; iii) claim 23 is confusing as it is apparently missing reference to what the mammal contains; iv) claim 25 is confusing as there is no SEQ ID NO: 28 disclosed.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claim 25 without prejudice or disclaimer to their right to pursue this claim in a later-filed application.

In addition, applicants respectfully traverse the Examiner's rejection with respect to claims 11, 23 and 29. Nevertheless, without conceding the correctness of the Examiner's rejection but to expedite prosecution of the subject application, applicants have

amended claims 11, 23 and 29 to address the Examiner's rejections. Applicants contend that these amendments obviate the above rejection. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

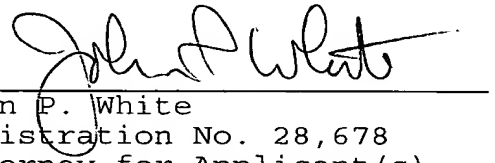
Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims, i.e. claims 11-14, 17-20, 23-24 and 26.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Preliminary Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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Marked-up Version of Amended Claims:

--11. (2X Amended) A transgenic non-human animal [carrying] comprising a recombinant [DNA] nucleic acid expression vector encoding a heterologous cholinesterase (ChE) enzyme selected from the group consisting of:

(a) wild-type human AChE;

(b) wild-type human BChE;

(c) variants of the AChE and BChE of (a) and (b); and

(d) [variants of the AChE and BChE of (a) and (b), said synthetic variants selected from recombinantly-produced point-mutated and deletion of one or more residues, mutations; and

(e)] wild-type insect ChEs[, said transgenic animal being capable of expressing amounts of said ChE enzyme for studying control of production on biochemical properties of cholinesterases],

wherein the nucleic acid is expressed in the germ cells and somatic cells of the transgenic animal.--

--12. (2X Amended) [A] The transgenic non-human animal [according to] of claim 11, wherein the animal is [selected from] *Xenopus* [and mice] or mammal.--

--13. (2X Amended) [A] The transgenic non-human animal [according to] of claim 12, [which carrying a] wherein the recombinant expression vector comprises a nucleic acid encoding a human AChE or a biologically active derivative[s] thereof [selected from], which nucleic acid comprises:

(a) [a DNA sequence which has all or part of the nucleotide] consecutive nucleotides having the nucleic acid sequence set forth in [()SEQ ID NO: 1[) as depicted in Figure 1A, and which encodes an amino acid sequence similar or identical to all or

part of the sequence of nucleic acid residues (SEQ ID NO: 20) depicted in Fig. 1B] or a fragment thereof;

(b) [a DNA sequence which has all or part of the nucleotide] consecutive nucleotides having the nucleic acid sequence[s] set forth in [(]SEQ ID NO: 3[) as depicted in Fig. 1C, and which encodes an amino acid sequence similar or identical to all or part of the sequence of amino acid residues (SEQ ID NO: 4) also depicted in Fig. 1C] or a fragment thereof; [and] or

(c) [A DNA sequence which has all or part of the nucleotide] consecutive nucleotides having the nucleic acid sequence set forth in [(]SEQ ID NO:5[) as depicted in Fig. 1D, and which encodes an amino acid sequence similar or identical to all or part of the sequence of amino acid residues (SEQ ID NO: 6) also depicted in Fig. 1D] or a fragment thereof.--

--14. (2X Amended) [A] The transgenic non-human animal [according to] of claim [13] 11, [in which said] wherein the recombinant expression vector [contains] comprises a promoter which [controlling] controls the transcription of [said] the nucleic acid sequence encoding AChE and is selected from the group of eukaryotic host cell compatible promoters.--

--17. (2X Amended) A transgenic non-human animal assay system for studying secretion, control of production and biochemical properties of cholinesterases in mammalian milk, comprising [a] the transgenic mammal [according to] of claim [11] 12.-

--18. (2X Amended) [A] The transgenic non-human mammal [according to] of claim [11] 12, [being] wherein the transgenic non-human mammal is capable of expressing amounts of ChE enzyme

in its mammary glands.--

--19. (2X Amended) The transgenic non-human [animal according to] mammal of claim 18, wherein [said] the ChE enzyme is [selected from the group consisting essentially of] wild-type human AchE[,] or a variant[s of AChE, and variants of the AchE] thereof.--

--20. (2X Amended) The transgenic non-human [animal according to] mammal of claim 19, wherein [said] the AChE variant[s are] is selected from the group consisting essentially of recombinantly-produced point mutation and deletion of one or more residues and mutations.--

--23. (2X Amended) [A] The transgenic [female] non-human mammal of claim 12, wherein the mammal is female and [said] the ChE enzyme expressed in the cells of the mammal is [selected from the group consisting of:

(i)] wild-type human AChE[;

(ii)] or a variant[s of AChE; and

(iii) variants of the AChE, said synthetic variants selected from recombinantly produced point mutated and deletion of one or more residues and mutations] thereof.--

--24. (2X Amended) A method of producing recombinant human AChE comprising the steps of:

(i) providing a lactating transgenic non-human [animal] female mammal according to claim[s] 23 [or 24];

(ii) obtaining milk from [the animal] the transgenic non-human mammal of step (i); and

(iii) isolating human AchE from the milk obtained in step (ii),

so as to thereby produce recombinant human AChE.--

--26. (New) The transgenic non-human animal of claim 12, wherein the mammal is a mouse.--